IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	Examiner: Landsman, Robert S.
Botstein, et al.	)	Art Unit: 1647
Application Serial No. 09/997,542	)	Confirmation No: 7269
Filed: November 15, 2001	)	Attorney's Docket No. 39780-2730 P1C26
For: **PRO1281 ANTIBODIES**	)	**Customer No. 35489**

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ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES
APPELLANTS' REPLY BRIEF

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

On August 11, 2005, the Examiner made a final rejection to pending Claims 119-121 and 123. A Notice of Appeal was filed on October 28, 2005, and an Appellants' Appeal Brief was filed January 26, 2006.

An Examiner's Answer was mailed on February 28, 2006. The following constitutes Appellants' Reply Brief in response to the Examiner's Answer and is timely filed. This Reply Brief is accompanied by a Request for Oral Hearing.

ARGUMENTS

I. *Claim Rejections Under 35 U.S.C. §101 and §112, First Paragraph*

Concerning the rejection of Claims 119-121 and 123 under 35 U.S.C. §101 as allegedly lacking a specific, substantial and credible asserted utility or a well established utility, in his Answer, the Examiner cites the following arguments:

(1) The Examiner did not find the Goddard declaration persuasive and says that "there is no statistical analysis disclosed, nor any formula disclosed showing how the data was analyzed in order to determine the significance of the amplification" (Examiner's Answer, page 5, lines 2-3) and that it "does not teach the level of reproducibility or the level of reliability of the results" (Examiner's answer, page 5, line 19-20). The Examiner further indicates that even if the 2-fold amplification for the genomic DNA encoding PRO1281 was significant, this does not provide any significance to the encoded protein (Examiner's answer, page 5, line 4-6). The Examiner also argues that Dr. Goddard, the expert, has interest in the outcome of the case because Dr. Goddard is employed by the assignee and is an inventor in this application (Examiner's answer, page 5, line 17-18).

(2) Regarding the Pennica reference, according to the Examiner what can be gathered is that, "based on the fact (in Pennica) that one gene increased in cancer and one did not, there is only a 50% chance of a gene increasing in a particular cancer...Therefore, given the fact that there is only a 50% chance of finding a gene which may be overexpressed in tumors and that this gene is not even overexpressed on every occasion (84%), it seems difficult to predict that a gene will be overexpressed" (Examiner's answer, page 6, line 8-13). The Examiner adds regarding the Konopka reference that it supports the Examiner's position because "Konopka *et al.* actually state that protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single pH template" (Examiner's answer, page 6, line 18-20). Referring to the Haynes reference, the Examiner says that "(g)iven the fact that Haynes is silent to DNA levels, it can be assumed, especially in light of Pennica and Konopka that DNA levels are not correlated (in general) to protein expression levels" (Examiner's answer, page 7, line 5-7).

(3) The Examiner has stated that Dr. Polakis' Declaration is allegedly not persuasive because "only conclusions are provided in the Declaration and does not provide data such that the Examiner can independently draw conclusions. There is no evidentiary support to the Polakis' statement that it remains a central dogma in molecular biology that increase mRNA levels are predictive of corresponding increased levels of the encoded polypeptide (Examiner's Answer, page 8, lines 11-14).

Appellants disagree with each of the Examiner's arguments on a number for grounds. The Examiner's arguments will be addressed in the order they are listed above.

Reply to the Examiner's arguments.

(1) The Examiner makes the rejection that "there is no statistical analysis disclosed, nor any formula disclosed showing how the data was analyzed in order to determine the significance of the amplification" (Examiner's Answer, page 5, lines 2-3). The Examiner's Answer concludes that "Dr. Goddard, the expert, has interest in the outcome of the case because Dr. Goddard is employed by the assignee and is an inventor in this application (Examiner's Answer, page 5, line 17-18).

Appellants submit that the Examiner is applying a standard that is not legally correct. The law, as it is reflected in the M.P.E.P. and the Utility Guidelines does not require that the Appellant show a positive result in a statistically large percentage of the tissue samples studied in order to make an assertion of utility. The above remarks by the Examiner are a clear indication that the Examiner applies a standard that might be appropriate, if the issue at hand were the regulatory approval of a diagnostic assay based on the overexpression of PRO1281 in lung tumor, but is fully inappropriate for determining if the "utility" standard of the Patent Statute is met. The FDA reviewing an application for a new diagnostic assay will indeed ask for actual numerical data, statistical analysis, and other specific information before a diagnostic assay is approved. However, the Patent and Trademark Office is not the FDA, and the standards of patentability are not the same as the standards for market approval. It is well established law that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to be marketed in the United States. *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994). Indeed, in *Nelson v.*

Bowler, 626 F.2d 853, 856, 206 USPQ 881, 883 (CCPA 1980), the Federal Circuit found that the identification of a pharmacological activity of a compound provides an "immediate benefit to the public" and satisfies the utility requirement. This logically applies to a diagnostic utility as well. The identification of a diagnostic utility for a compound should suffice to establish an "immediate benefit to the public" and thus to establish patentable utility.

Further, the Goddard Declaration was presented to show what ΔCt values were considered significant in the TaqMan™ assay. The ΔCt values for PRO1281 of at least 1.07-1.15Ct units, which correspond to **2.099 fold to 2.219-fold** amplification in primary colon tumors, were considered significant according to the Goddard declaration. The formula for showing how the data was analyzed has been clearly disclosed in the specification in Example 170, page 539. As explained in the passage on page 539, lines 37-39, "the results of TaqMan™ PCR are reported in ΔCt units. **One unit** corresponds to one PCR cycle or approximately a **2-fold amplification**, relative to control, two units correspond to 4-fold, 3 units to 8-fold amplification and so on" (emphasis added). Table 9C indicates that PRO1281 showed approximately 1.07-1.15 ΔCt units which corresponds to $2^{1.07}$ -$2^{1.15}$- fold amplification or **2.099 fold to 2.219-fold** amplification in colon tumors, which is significant and thus the PRO1281 gene has utility as a diagnostic marker of human colon cancer.

Further, Dr. Goddard's declaration is based on Dr. Goddard's personal experience handling large databases of human tumor samples in the SPDI project and on personal experience with the TaqMan™ assay, as is clearly disclosed in the Declaration. The Examiner cannot disregard this declaration simply because Dr. Goddard works for the Assignee. Instead, the Examiner has to view the statements in the declaration with the total evidence presented in this case. The case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew.[1] "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record,

[1] *In re Rinehart*, 531 F.2d 1084, 189 USPQ 143 (C.C.P.A. 1976); *In re Piasecki*, 745 F.2d. 1015, 226 USPQ 881 (Fed. Cir. 1985).

by a preponderance of the evidence with due consideration to persuasiveness of argument."[2] Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an Examiner."[3] Appellants also respectfully draw the Examiner's attention to the Utility Examination Guidelines[4] which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered."

Appellants submit that the Patent Office has failed to provide substantial evidence for disregarding the Goddard Declaration.

(2) Regarding the Examiner's rejections based on Pennica *et al.*, and Konopka *et al.*, as has been discussed throughout prosecution and in the Appeal Brief filed January 26, 2006, Appellants maintain that Pennica *et al.* analyzed three specific WISP genes and Konopka *et al.* analyzed one specific gene, the *abl* gene, and their conclusions are based on and limited to the specific genes studied. There is nothing in these references that would suggest that the authors intended to draw broader conclusions from their findings. Therefore, Pennica *et al.* and Konopka *et al.* cannot be used as evidence of a poor correlation between mRNA and protein levels because these references did not show or suggest that, **in general**, it is more likely than not for mRNA and protein levels not to have a correlation. The detailed reasons were clearly discussed in the Appeal Brief. Further, Appellants clearly discussed in the Appeal Brief and throughout prosecution that Haynes *et al.* in fact support the Appellants position that it is more likely than not for mRNA and protein levels to have a correlation based at least on the results shown in Figure 1 where, most of Haynes *et al.*'s data points showed a general trend in increase in protein expression for a corresponding mRNA data point. Appellants also pointed out that

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[2] *In re Alton,* 37 USPQ2d 1578, 1584 (Fed. Cir 1996) (quoting *In re Oetiker,* 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992)).

[3] *In re Alton, supra.*

[4] Part IIB, 66 Fed. Reg. 1098 (2001).

accurate prediction of protein levels from mRNA levels was not needed to make the prediction that that it is more likely than not for mRNA and protein levels to have a correlation. The Examiner's arguments have not met the burden of proof for a *prima facie* showing based on Pennica *et al.*, Konopka *et al.*, and Haynes *et al.*

On the other hand, Appellants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded mRNA will be expressed at an elevated level. First, the articles by Ornfoft *et al.*, Hyman *et al.*, and Pollack *et al.*, (made of record in Appellants' Response filed June 4, 2004) collectively teach that in general, gene amplification increases mRNA expression.

The Examiner argues that the Ornfoft *et al.* reference "concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes....the relevance, if any of Ornfoft *et al.* is not clear" (Examiner's Answer, page 8, line 6-10). Appellants submit that Ornfoft *et al.* studied 1,800 genes that yielded an increase or decrease in mRNA expression in two invasive tumors compared to the two non-invasive papillomas were then mapped to chromosomal locations. The chromosomes had already been analyzed for amplification by hybridizing tumor DNA to normal metaphase chromosomes (CGH). Ornfoft *et al.* used CGH alterations as the independent variable and estimated the frequency of expression alterations of the 1,800 genes in the chromosomal areas. Ornfoft *et al.* found that in general (77% and 80% concordance) areas with a strong gain of chromosomal material contained a cluster of genes having increased mRNA expression (see page 40). Ornfoft *et al.* state, "For both tumors TCC733 ($p<0.015$) and TCC827 ($p<0.00003$) a highly significant correlation was observed between the level of CGH ratio change (reflecting the DNA copy number) and alterations detected by the array based technology" (see page 41, column 1). Ornfoft *et al.*, also studied the relation between altered mRNA and protein levels using 2D-PAGE analysis. Ornfoft *et al.* state, "In general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations.... 26 well focused proteins whose genes had a known chromosomal location were detected in TCCs 733 and 335, and of these 19 correlated ($p<0.005$) with the mRNA changes detected using the arrays." (See page 42, column 2 to page 34, column 2). Accordingly, Ornfoft *et al.* clearly support Appellants' position that proteins expressed by genes that are

amplified in tumors are useful as cancer markers. Also, Orntoft *et al.* did not limit their findings to only those regions of amplified gene clusters.

Therefore, as explained above, Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* were presented to show that in general, gene amplification increases mRNA expression.

(3) To establish the correlation, in general, between increased mRNA and increased protein expression levels, Appellants presented the Polakis Declaration (made of record in Appellants' Response filed June 4, 2004). According to the Examiner Dr. Polakis' Declaration is not persuasive because "only conclusions are provided in the Declaration and does not provide data such that the Examiner can independently draw conclusions" (Examiner's Answer, page 8, lines 11-14). The Examiner's position is factually and legally incorrect.

But Dr. Polakis explains in his declaration that, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. Accordingly, Dr. Polakis has provided facts that the Examiner has no reason to doubt. As discussed earlier, a patent Examiner must accept statements made in an expert declaration, unless there are serious doubts to question there. In the present case, there is absolutely no foundation for any doubt, and such, the Examiner's objections are misplaced.

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule. In the majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack

et al., and the Polakis Declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1281 gene, that the PRO1281 polypeptide is concomitantly overexpressed. Thus, Appellants submit that the PRO1281 polypeptides and antibodies have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use the antibody for diagnosis of cancer.

II. *Claim Rejections Under 35 U.S.C.§112, First Paragraph- Enablement*

Appellants maintain, for the reasons set forth in the Appeal brief filed January 26, 2006, that the genus of claimed polypeptides of Claims 119-121 and 123 is further defined by having a specific functional activity for the encoding nucleic acids, namely, that the encoding nucleic acid is amplified in colon tumors. The specification provides detailed guidance as to how to identify the recited variants of SEQ ID NO:326, including methods for determining percent identity between two amino acid sequences, as well as listings of exemplary and preferred sequence substitutions, as well as detailed protocols for determining whether a gene encoding a variant PRO1281 protein is amplified in colon tumor. Thus one of skill in the art could easily identify whether a variant PRO1281 sequence falls within the parameters of the claimed invention and that the instant specification sufficiently provides enablement to the skilled artisan.

III. *Claim Rejections Under 35 U.S.C.§102*

Appellants maintain, for the reasons set forth in the Appeal brief filed January 26, 2006, that priority application, U.S. provisional application 60/141,037 has utility based on the gene amplification assay, and thus Claims 119-121 and 123 are entitled to the priority date of June 23, 1999. Therefore, Tang et al. is not prior art.

IV. *Claim Rejections Under 35 U.S.C.§103*

Appellants maintain, for the reasons set forth in the Appeal brief filed January 26, 2006, that priority application, U.S. provisional application 60/141,037 has utility based on the gene amplification assay, and thus Claims 119-121 and 123 are entitled to the priority date of June 23, 1999. Therefore, Tang *et al.* is not prior art and therefore this 103 rejection falls based on

Tang *et al.* Further, Weimann *et al.* does not teach the instantly claimed subject matter and hence this reference also falls. Therefore, this rejection under 103 should be withdrawn.

CONCLUSION

For the reasons given above, Appellants submit that present specification clearly describes, details and provides a patentable utility for the claimed invention. Moreover, it is respectfully submitted that based upon this disclosed patentable utility, the present specification clearly teaches "how to use" the presently claimed polypeptide. As such, Appellants respectfully request reconsideration and reversal of the outstanding rejection of Claims 119-121 and 123.

The Commissioner is authorized to charge any fees which may be required, including extension fees, or credit any overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2730 P1C26**).

Respectfully submitted,

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